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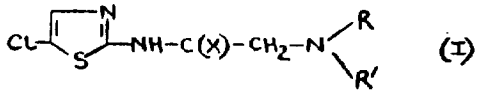
(19)

(54) 2-AMINO-5-CHLORO-THIAZOLE DERIVATIVES

(71) We, MELLE-BEZONS, a French Body Corporate, of 79 Saint-Leger-les-Melle, (Deux-Sevres), France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to substituted thiazole compounds and more particularly to 2-amino-5-chloro-thiazole derivatives having therapeutic properties, to a process for the preparation of such compounds and to therapeutic compositions containing them.

In accordance with the invention there is provided a thiazole compound having the general formula:



(I)

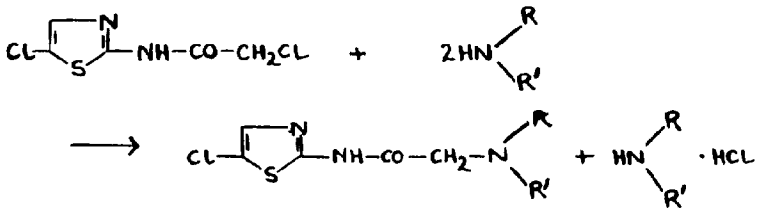
in which X represents O or H_2, and each of R and R′, which may be the same or different, is an alkyl, aralkyl, heterocyclic or (heterocyclo)alkyl group or R′ may be a hydrogen atom; or R and R′, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group.

It should be noted that groups R and/or R′, or the nitrogen-containing heterocyclic group which they form with the nitrogen atom, may bear one or more substituents, more particularly, but without limitation, alkyl, aryl, hydroxy, hydroxyalkyl or alkoxyalkyl groups, or halogen atoms. It should also be noted that when R and/or R′ are heterocyclic groups, these may comprise more than one hetero atom selected from N, O and S; likewise, when R and R′ form a heterocyclic group which includes the nitrogen atom, this group may comprise at least one other hetero atom selected from N, O and S.

More particularly, R and/or R′ may be, or where appropriate form together with the nitrogen atom, any one of the following groups, methyl, ethyl, isopropyl, *n*-butyl, *sec*-butyl, hydroxyethyl, methoxyethyl, methoxypropyl, benzyl, phenylethyl, phenylpropyl, 2-thiazolyl, 5-chloro-2-thiazolyl, piperidyl, piperazinyl, N′-(hydroxyethyl) piperazinyl, phenylpiperazinyl, N′[N-(5-chloro-2-thiazolyl)-2-aminoethyl]-piperazinyl, N′-[N-(5-chloro-2-thiazolyl) acetamido] piperazinyl, morpholinyl, and methylmorpholinyl.

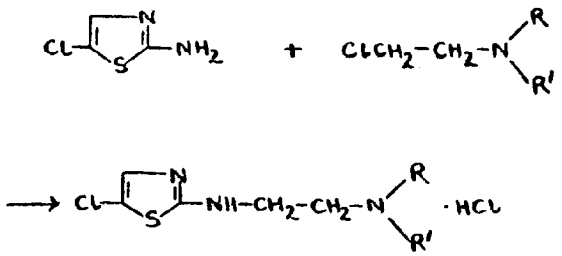
For example, according to the nature of R and R′, it is possible to have compounds in accordance with the above general formula (I), in which the substitutions on the nitrogen atom bearing R and R′ will give combinations such as: di-methyl, di-ethyl, di-isopropyl, mono-ethyl, mono-isopropyl, methyl+*n*-butyl, mono-*sec*-butyl, bis-(hydroxyethyl), mono-(hydroxyethyl), methyl+hydroxyethyl, mono-(2-methoxyethyl), mono-(3-methoxypropyl), mono-benzyl, mono-(2-phenylethyl), mono-(3-phenylpropyl), mono-(2-thiazolyl), mono-(5-chloro-2-thiazolyl), piperidyl, piperazinyl, N′-(hydroxyethyl) piperazinyl, 4-phenylpiperazinyl, N′-[N-(5-chloro-2-thiazolyl)-2-aminoethyl] piperazinyl, N′ - [N - (5 - chloro - 2 - thiazolyl) acetamido] piperazinyl, morpholinyl and 2-methylmorpholinyl.

The compounds according to the invention in which C(X) represents the carbonyl group, CO, may be prepared, particularly, by the reaction of 2-chloroacetamido-5-chlorothiazole with a suitable amine of the formula R—NH—R′ (R and R′ being as above defined), this amine being preferably employed in an amount approximately twice, or even above twice, the stoichiometric amount. At least a part of the excess amine serves to fix the hydrogen chloride liberated by the reaction, according to the equation:

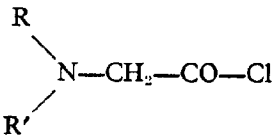


To fix or neutralize the hydrogen chloride alternatively, there may be used an alkaline acid-acceptor which takes no part in the main reaction, for example either a tertiary amine such as triethylamine, or an alkali metal carbonate such as potassium carbonate.

The compounds according to the invention in which C(X) represents the methylene group, CH_2, may be prepared, particularly, by the reaction of 2-amino-5-chloro-thiazole with a suitable chlorethylamine. In such a case the product obtained is generally basic enough to be able to serve as an acceptor for the hydrogen chloride liberated by the reaction, for example:—



By applying conventional processes, variations may be introduced into the above-specified preparation methods, which constitute only illustrative, non-limiting examples. Thus, for the compounds in which X is O, it is possible first to prepare by conventional techniques a substituted glycinyl chloride having the following formula:—



and then to react this chloride with 2-amino-5-chloro-thiazole.

It is also possible to obtain the compounds in which X is H_2 by first preparing, by conventional techniques, N - [2 - (2 - hydroxy - ethylamino)] - 5 - chloro - thiazole, then converting the same, by conventional techniques, to N-[2-(2-chloroethyl) amino]-5-chloro-thiazole and reacting the latter with an excess of a suitable amine of formula R—NH—R′.

From the physiological standpoint, the compounds according to the present invention are characterized by a low toxicity and a good gastric tolerance, which allow them to be used in therapeutic compositions.

Thus the invention also provides a therapeutic composition comprising, as the active ingredient, a compound having the general formula (I) herein, in admixture with a pharmacologically acceptable carrier.

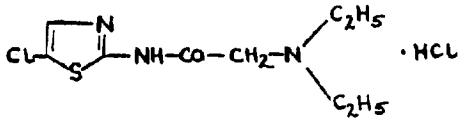
In the therapeutic field the compounds of formula (I) have, particularly, sedative, tranquillizing and analgesic properties. In accordance with a preferred use, they are employed as anti-inflammatory agents.

In particular, it often happens that anti-inflammatory agents belonging to other chemical classes suffer from the drawback of a bad gastric tolerance. Certain of them may even give rise to ulcers and this necessitates precautions, and results in restrictions in their clinical applications.

The following Examples illustrate the preparation of compounds according to the invention.

Example 1

Preparation of the hydrochloride of 5-chloro-2-diethylamino-acetamido-thiazole, having the following formula:—



15 grams of 2-chloroacetamido-5-chloro-thiazole, i.e. 71 millimoles, is dissolved in 100 ml of boiling benzene. There is slowly added to the solution, while stirring it, 13 g of diethylamine, i.e. 71 millimoles. The resulting mixture is energetically stirred, boiled for 3 hours under reflux and then allowed to settle for 12 hours.

The crystalline precipitate of triethylamine hydrochloride which has formed is separated by filtration and the filtrate is evaporated to dryness under vacuum. The residue of the evaporation is dissolved in acetone, and dry hydrogen chloride is passed through the resulting solution. 5-Chloro-2-diethylaminoacetamido-thiazole hydrochloride precipitates and is drained under vacuum and dried. It is finally re-crystallized from its solution in acetonitrile.

There is so obtained 12.9 g of final product, i.e. a yield of 65%. This product exhibits the following characteristics:

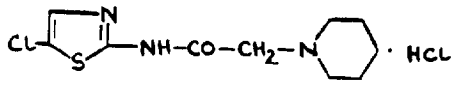
Melting point: 155°C.

Elementary analysis (percentages):

	C	H	Cl	N
Found:	38.11	5.25	24.99	14.80
Calculated:	38.03	5.32	24.95	14.78

Example 2

Preparation of the hydrochloride of 5-chloro-2-(1-piperidyl-acetamido) thiazole, having the following formula:—



The method is analogous to that of Example 1.

30 g of 2-chloroacetamido-5-chloro-thiazole, i.e. 0.14 mole, is dissolved in 500 ml of acetonitrile. Into the solution, stirred and boiled under reflux, there is introduced drop by drop 23.8 g of piperidine, i.e. 0.28 mole, and then the stirring and heating are continued for one hour after this introduction. The reaction mixture is then cooled, the crystals formed are filtered and water-washed till complete removal of the piperidine hydrochloride formed is achieved. The filtrate is concentrated, which permits recovery of a second fraction of crystals which is washed as the first one and mixed therewith.

The mixture of these two fractions is purified by dissolving in a 50/50 ethanol/water mixture, treatment of the boiling aqueous alcoholic solution by charcoal, and re-crystallization by cooling of the solution to 0°C. There is so obtained 26.5 g of a white crystalline powder constituting the desired product, but in basic form. The yield amounts to 72%. The product exhibits the following characteristics:

Melting point: 139°C.

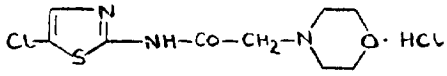
Elementary analysis (percentages):

	C	H	Cl	N	S
Found:	46.24	5.52	13.93	16.29	12.14
Calculated:	46.24	5.43	13.65	16.17	12.34

As in the preceding example, the hydrochloride of the base is obtained by bubbling hydrogen chloride through a solution of the base in acetone. The hydrochloride yield amounts to 96% with respect to the base. The melting point of the hydrochloride is 237°—238.5°C.

Example 3

Preparation of the hydrochloride of 5-chloro-2-(4-morpholinyl-acetamido) thiazole, having the following formula:



The operation is analogous to that of Example 2. There is used 42 g of 2-chloracetamido-5-chloro-thiazole, i.e. 0.2 mole, 35 g of morpholine, i.e. 0.4 mole, and 600 ml of acetonitrile. The raw base is directly dissolved in acetone and is converted to the hydrochloride as described in Example 2. The hydrochloride is drained and dried under vacuum. There is obtained 40.2 g of white, fine needles constituting the desired final product, i.e. a yield of 65%. This product exhibits the following characteristics:

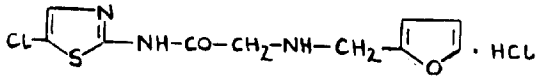
Melting point: 256°C.

Elementary analysis (percentages):

	C	H	Cl	N	S
Found:	36.08	4.24	23.79	14.12	10.74
Calculated:	36.25	4.39	23.78	14.09	10.75

Example 4

Preparation of the hydrochloride of 5-chloro-2-furfurylamino-acetamido-thiazole, having the following formula:—



There is used a method analogous to that of Example 3, starting from 24 g of 2-chloroacetamido-5-chloro-thiazole and 25.5 g of furfurylamine. There is obtained 23.4 g of a white powder constituting the desired final product, i.e. a yield of 67%. This product exhibits the following characteristics:

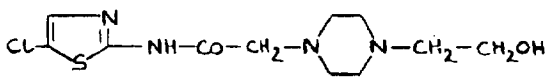
Melting point: 203°C.

Elementary analysis (percentages):

	C	H	Cl	N	S
Found:	38.93	3.61	22.91	13.20	10.20
Calculated:	38.97	3.60	23.01	13.63	10.40

Example 5

Preparation of 5-chloro-2-[4-[(2-hydroxyethyl)-1-piperazinyl] acetamido] thiazole, having the following formula:—



42 g of 2-chloracetamido-5-chloro-thiazole is dissolved in 600 ml of boiling acetonitrile. There is then introduced into the stirred, boiling solution 52 g of N-(2-hydroxyethyl) piperazine and the resulting mixture is boiled under reflux for one hour. It is then cooled and the resulting precipitate is separated by filtration and water-washed until chloride anions have completely disappeared from the washing liquid. The precipitate is finally re-crystallized from its solution in 95 vol.% ethanol.

There is obtained 44 g of bright, white crystals constituting the desired final product, i.e. a yield of 71%. This product exhibits the following characteristics:

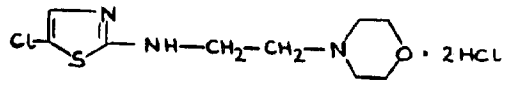
Melting point: 138°C.

Elementary analysis (percentages):

	C	H	Cl	N	S
Found:	43.42	5.75	11.85	18.25	10.57
Calculated:	43.34	5.62	11.63	18.38	10.52

Example 6

Preparation of the di-hydrochloride of N-[2-[(5-chloro-2-thiazolyl) amino]-ethyl] morpholine, having the following formula:—



9.3 g of N-(2-chloroethyl) morpholine hydrochloride, i.e. 50 millimoles, is dissolved in water, the solution is heated to 70°C. and, while maintaining this temperature, there is introduced thereinto 6.73 g of 2-amino-5-chloro-thiazole, i.e. 50 millimoles. Then the temperature is still maintained at the same value for 4 hours and, after decolorizing the solution by means of activated carbon, this solution is concentrated by evaporation under vacuum. The residue of the evaporation is comminuted in boiling ethanol. The remaining, insoluble substance is the desired di-hydrochloride.

This substance may be purified by dissolving it in water and again treating the solution with activated carbon. The clear solution is then evaporated to dryness and the residue is treated with boiling ethanol. The remaining, solid final product exhibits the following characteristics:

Melting point: 256°C.

Elementary analysis (percentages):

	C	H	Cl	N	S
Found:	33.13	5.11	32.80	12.57	9.57
Calculated:	33.71	5.03	33.16	13.13	10.00

Physiological properties:

Toxicity:

There is given below a number of values of the LD_{50} determined by the Behrens and Karber method on mice:—

	LD_{50} (mg/kg) Through the peritoneal route	Through the oral route
Product of Example 1	120	240
" " " 2	37	250
" " " 3	575	1750
" " " 4	350	1700
" " " 5	950	2000
" " " 6	475	1400

Thus, it can be seen that these various products have a very low toxicity, more especially through the oral route.

Anti-inflammatory activity:

This activity is determined by the conventional method of the kaolin oedema test on mice.

In the kaolin oedema-test groups of 10 mice are tested.

Each one of the mice is given an injection of 0.1 ml. of a kaolin suspension at 10% in one of the rear paws, the other paw serving as a control. The first group serving as control is not given any treatment after the injection.

The second group receives, two hours after the injection, a dose of 50 mg/kg of Δ-hydrocortisone, as a control product. The other groups are given, two hours after the injection, doses of the products to be tested.

After 24 hours the animals are killed, and their rear paws are weighed. The

comparison, in each group, between the weight of paws having received the kaolin injection and that of the control paws, gives a percentage of inflammation.

Where P_1 is the percentage of inflammation of the paws of the untreated mice (group 1), and

P_2 is the percentage of inflammation of the mice treated with hydrocortisone or with the products to be tested (group 2 and following),

the anti-inflammatory activity is calculated according to the following formula:

$$\left(\frac{P_1}{P_2} - 1\right) \times 100$$

and expressed as a percentage.

The activity results are given in the following Table (the products having been administered through the digestive tracts):—

	Amount (mg/kg)	Anti-inflammatory activity
Product of Example 1	25	21.7%
	50	33.2%
Product of Example 2	25	27.3%
	50	39.8%
Product of Example 3	50	24.6%
	175	38.8%
Product of Example 4	50	27.1%
	170	38.4%
Product of Example 5	50	22.6%
	200	29.7%
Product of Example 6	50	31.7%
	100	34.2%
Δ Hydrocortisone (reference product)	50	24.1%

Thus, the products of the present invention exhibit a high therapeutic index.

Determination of aggressiveness towards gastric mucous membranes:

Groups of ten rats, previously subjected to a 24-hour fast, received through the digestive tracts, either the product of Example 1, in amounts of 25, 50 and 100 mg/kg respectively, or the product of Example 6, in amounts of 50, 100 and 200 mg/kg respectively, or O-acetylsalicylic acid in amounts of 200 and 400 mg/kg respectively.

For the products of Examples 1 and 6, these amounts correspond to a pronounced anti-inflammatory activity, O-acetylsalicylic acid, on the other hand, being perceptibly active only in an amount of 400 mg/kg.

Four hours later, the animals were killed and their stomachs were examined.

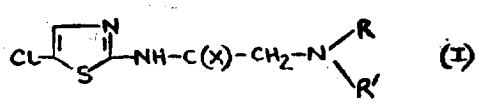
With the products of Examples 1 and 6, no ulceration was found for any of the amounts used. With O-acetylsalicylic acid, there was found:

for 200 mg/kg: 30% ulceration;
for 400 mg/kg: 70% ulcerations.

N.B. The rate of ulceration is the proportion, expressed in percentage of the rats, of each lot having stomach ulcers, after administration of the doses of the products to be tested.

WHAT WE CLAIM IS:—

1. A thiazole compound having the general formula:



(I)

in which X represents O or H_2, and each of R and R', which may be the same or

different, is an alkyl, aralkyl, heterocyclic or (heterocyclo) alkyl group, or R′ may be a hydrogen atom or R and R′, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group.

2. A compound according to claim 1, wherein the groups R and/or R′, or the nitrogen-containing heterocyclic group which they form with the nitrogen atom bear one or more substituents.

3. A compound according to claim 2, wherein the substituent or substituents is or are alkyl, aryl, hydroxy, hydroxyalkyl or alkoxyalkyl groups, or halogen atoms.

4. A compound according to any one of claims 1 to 3, wherein R and/or R′ is or are heterocyclic groups comprising more than one hetero atom selected from N, O and S.

5. A compound according to any one of claims 1 to 3, wherein R and R′ together with the nitrogen atom, form a heterocyclic group which also contains at least one other hetero atom selected from N, O and S.

6. A compound according to any one of claims 1 to 5, wherein R and/or R′ is or are, or where appropriate form together with the nitrogen atom, any one of the following groups, methyl, ethyl, isopropyl, *n*-butyl, *sec*-butyl, hydroxyethyl, methoxyethyl, methoxypropyl, benzyl, phenylethyl, phenylpropyl, 2-thiazolyl, 5-chloro-2-thiazolyl, piperidyl, piperazinyl, N′-(hydroxyethyl) piperazinyl, phenylpiperazinyl, N′ - [N - (5 - chloro - 2 - thiazolyl) - 2 - aminoethyl] piperazinyl, N′ - [N - (5 - chloro - 2 - thiazolyl) - acetamido] piperazinyl, morpholinyl and methylmorpholinyl.

7. A process for the preparation of a compound having formula (I) herein in which X represents O, which comprises reacting 2-chloracetamido-5-chloro-thiazole with an amine having the formula R—NH—R′, in which R and R′ are as defined in claim 1.

8. A process according to claim 7, wherein the amine, R—NH—R′, is employed in an amount approximately twice, or above twice, the stoichiometric amount.

9. A process according to claim 7, wherein the reaction is carried out in the presence of an alkaline acid-acceptor which takes no part in the main reaction.

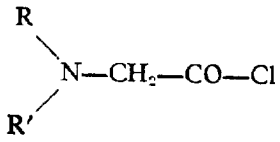
10. A process according to claim 9, wherein the acid-acceptor is a tertiary amine.

11. A process according to claim 10, wherein the tertiary amine is triethylamine.

12. A process according to claim 9, wherein the acid-acceptor is an alkali metal carbonate.

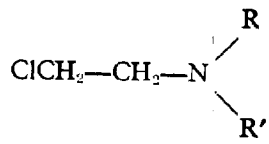
13. A process according to claim 12, wherein the alkali metal carbonate is potassium carbonate.

14. A process for the preparation of a compound having formula (I) herein, in which X represents O, which comprises reacting a substituted glycinyl chloride having the formula:



in which R and R′ are as defined in claim 1, with 2-amino-5-chlorothiazole.

15. A process for the preparation of a compound having formula (I) herein, in which X represents H_2, which comprises reacting 2-amino-5-chloro-thiazole with a chlorethylamine having the following formula:



in which R and R′ are as defined in claim 1.

16. A process for the preparation of a compound having formula (I) herein, in which X represents H_2, which comprises reacting N-[2-(2-chloroethyl) amino]-5-chloro-thiazole, with an excess of an amine having the formula R—NH—R′, in which R and R′ are as defined in claim 1.

17. A therapeutic composition comprising, as the active ingredient, a compound having the general formula (I) herein, in admixture with a pharmacologically acceptable carrier.

18. A 2-amino-5-chloro-thiazole compound having the general formula (I) herein substantially as hereinbefore described with reference to the Examples.

19. Processes for the preparation of 2-amino-5-chloro-thiazole compounds having the general formula (I) herein substantially as hereinbefore described with reference to the Examples.

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